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10/010,749	12/06/2001	Jean-Louis Escary	21349/5	2921

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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/010,749	ESCARY, JEAN-LOUIS	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *15 and 17-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/6/01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0402* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed May 23, 2003. Currently, claims 1-25 are pending. Claims 15, 17-25 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election with traverse of Group I (Claims 1-14, 16) in the paper filed May 23, 2003 is acknowledged. The traversal is on the ground(s) that there will not be a serious burden on the examiner if restriction is not required since the groups are closely related and will substantially overlap. This is not found persuasive because dependent inventions may be properly restricted if they are distinct. As discussed in MPEP 803, one of the two criteria for requirement of restriction is that the "inventions must be independent (see MPEP 802.01, 806.04, 808.01) or distinct as claimed". Accordingly, the demonstration of distinctness of the inventions is sufficient grounds for restriction. As stated in MPEP 802.01 "(t)he law has long been established that dependent inventions (frequently termed related inventions) such as those used for illustration above may be properly divided if they are, in fact "distinct" inventions, even though dependent". Further, it would be an undue burden to examine the claims of all Groups I-VIII because not all of the groups have acquired the same status in the art. This is recognized by their different classification and as recognized by their divergent subject matter and because a search of the subject matter of invention 1 is not co-extensive with a search of inventions II-VIII. A search for the method of determining at

least one functional SNP is not a coextensive search of a composition comprising a polynucleotide and a carrier.

The requirement is still deemed proper and is therefore made FINAL.

Claims 15, 17-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

This application contains claims 15, 17-25 are drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

3. This application claims priority to foreign filed France 0015838, filed 12/6/00.

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

Drawings

4. The drawings are acceptable.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 8, 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 8 is indefinite over the recitation "(in silico)" and (in vivo or in vitro)" because it is unclear whether the phrases within the parentheses further limit the claim. It is not clear how these phrases impart limitations to the instant claims. In the event that the claims are intended to include these phrases as limitations to the claims, the claims may be amended to recite "in silico bioinformatic molecular modeling" and "in vivo or in vitro biological assays."

B) Claim 16 is indefinite because it is unclear as to whether the claims are intended to be limited to methods of a method for generating a map of genetic markers or a method of a method for identifying functional SNPs. The claims are drawn to a method for generating a map of genetic markers. However, the Claim refers back to Claim 1 which has a final step directed to identifying functional SNPs. Accordingly, it is unclear as to whether the method is a method of generating a map of genetic markers

or a method of identifying functional SNPs. Upon identifying functional SNPs it is unclear how a map of genetic markers is generated.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 3-5, 8-9, 16, are rejected under 35 U.S.C. 102(b) as being anticipated by Dresdale et al (PNAS, Vol. 97, No. 19, pages 10483-10488, September 12, 2000).

Drysdale et al. (herein referred to as Drysdale) teaches analyzing various combinations of SNPs to identify those with functionality. Specifically Drysdale teaches selecting the human B2-adrenergic receptor gene, providing a sample of individuals from a index repository of "apparently normal individuals", isolating the B2AR gene, identifying thirteen SNPs in the B2AR gene which were organized into 12 haplotypes; and performed an analysis of protein and mRNA expression to determine functionality. Drysdale teaches sampling "normal individuals" from a repository consisting of 23 Caucasians, 19 African Americas, 20 Asians, and 15 Hispanic Latinos (Table 1 and page 10485, col. 1, para 2). These individuals do not have any particular genotype or phenotype which is "known" (limitations of Claim 3). Drysdale teaches using the reference sequence for the intronless human B2AR gene (Genbank Accession

M15169)(page 10484, col. 1). The PCR products using genomic DNA as template were sequenced (page 10484, col. 2)(limitations of Claim 5). Drysdale teaches identifying 8 SNPs in the 5' UTR and 5 additional SNPs, three of which alter the encoded residues in the protein (Table 1, page 10484, col. 1)(limitations of Claim 16). The PCR products from the B2AR gene were placed in a vector and receptor expression was determined by radioligand binding, and mRNA levels were determine by using ribonuclease protection assays (page 1484, col. 2)(limitations of Claim 4, 8-9). Dresdale states that for both protein and mRNA expression, the results of the study are entirely consistent with the in vivo findings. Dresdale concludes that "the results indicate that the unique interactions of multiple SNPs within a haplotype ultimately affect biologic and therapeutic phenotype" (page 10488, col. 2). Since, Dresdale teaches every limitation of the instant claims, Dresdale anticipates the instant claims.

7. Claims 1-5, 8, 16, are rejected under 35 U.S.C. 102(a) as being anticipated by Nandabalan et al. (WO 00/50436, August 31, 2000).

Nandabalan et al. (herein referred to as Nandabalan) teaches a method of identifying functional SNPs in a gene. Nandabalan selects a candidate gene, namely tissue necrosis factor receptor (TNFR1). Nandabalan samples a "normal population" of individuals whose genomic DNA was isolated from an Index Repository containing 150 human individuals (page 5, lines 34-36). The human individuals comprise 112 unrelated individuals from African, Asian, Caucasian and Hispanic/Latino descent (Table 1, page 6)(limitations of Claim 2-3). Nandabalan teaches isolating nucleic acid

from the individuals using PCR primers and identifying at least on SNP within the nucleic acid, namely 12 polymorphic sites (Table 5, page 38). Nandabalan also identifies which of the mutations change the coding sequence, thereby which SNPs are functional. Nandabalan teaches that allele-specific oligonucleotide primes may be used to detect TNFR1 gene polymorphisms (page 19). Nandabalan teaches that the effects of the polymorphism identified on expression of TNFR1 may be investigated by preparing recombinant cells (page 15, lines 29-35). Nandabalan exemplifies amplifying various regions of the TNFR1 gene using primers (page 30). The PCR products were sequenced in both directions and analyzed for the presence of the polymorphisms (page 32-33)(limitations of Claims 4-5). Nandabalan also provides Table 4 indicating observed genotypes and haplotype pairs for TNFR1 (page 35). Figure 4 illustrates the SNPs within the coding sequence and Figure 5 illustrates the SNPs which alter the protein sequence (limitations of Claim 8, 16). The SNPs which alter the protein sequence are functional to the extent that the protein sequence is altered, i.e. modifies the functionality of the preselected candidate gene (as defined in the instant specification, paragraph 93). Since, Nandabalan teaches every limitation of the instant claims, Nandabalan anticipates the instant claims.

8. Claims 1, 3-5, 8-9 are rejected under 35 U.S.C. 102(a) as being anticipated by Gu et al. (JBC Papers in Press. Published on January 9, 2001 as Manuscript M010353200).

Gu teaches a method of determining at least on functional SNP in a gene by selecting a candidate gene, namely P2X7 receptor, sampling a "normal population", isolating nucleic acid from the individuals, identifying at least on SNP and identifying functional SNPs. Gu teaches studying P2X7 by sequencing DNA coding for the carboxyl terminal tail of P2X7. Peripheral blood lymphocytes and monocytes were obtained from 45 normal subjects (page 6)(limitations of Claim 3). Genomic DNA was extracted using a primer pair and amplified (page 7). The amplified PCR products were sequenced using electrophoresis (page 7)(limitations of Claims 4-5). A nucleotide substitution (A1513C) was found which cause a substitution for glutamic acid to alanine at amino acid position 496 (abstract, page 2). Gu teaches performing site directed mutagenesis to introduce a mutant (page 8). The functionality of the two sequences were analyzed (page 9). The function of the P2X7 receptors expressed on lymphocytes and monocytes was compared with the genotype at position 1513 of the P2X7 gene (page 10)(limitations of Claims 8-9). Cells transfected with germline and A1513C mutation were analyzed for surface expression by quantitating binding of FITC-conjugated mAb and the ATP-induced uptake of ethidium (page 11). Gu concludes that the "data in this study shows that the function of the human P2X7 receptor is affected by the single nucleotide mutation of adenine to cytosine at position 1513 of cDNA which changes glutamic acid to alanine at amino acid position 496" (page 13). The analysis demonstrated that homozygosity (C/C) for this polymorphic mutation let to almost complete loss of P2X7 function in leukocytes while herterozygosity (A/C) gave a function which was half that of cells with the germline P2X7 sequence (page 13).

Therefore, since Gu teaches every limitation of the instant claims, Gu anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 6, 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dresdale et al (PNAS, Vol. 97, No. 19, pages 10483-10488, September 12, 2000) or Nandabalan et al. (WO 00/50436, August 31, 2000) or Gu et al. (JBC Papers in Press. Published on January 9, 2001 as Manuscript M010353200) in view of Apffel et al. (US Pat. 6,379,889, April 30, 2002).

Drysdale et al. (herein referred to as Drysdale) teaches analyzing various combinations of SNPs to identify those with functionality. Specifically Drysdale teaches selecting the human B2-adrenergic receptor gene, providing a sample of individuals from a index repository of "apparently normal individuals", isolating the B2AR gene, identifying thirteen SNPs in the B2AR gene which were organized into 12 haplotypes; and analysis of protein or mRNA expression to determine functionality. Drysdale teaches sampling "normal individuals" from a repository consisting of 23 Caucasians, 19 African Americas, 20 Asians, and 15 Hispanic Latinos (Table 1 and page 10485, col. 1, para 2). These individuals do not have any particular genotype or phenotype which is

"known" (limitations of Claim 3). Drysdale teaches using the reference sequence for the intronless human B2AR gene (Genbank Accession M15169)(page 10484, col. 1). The PCR products using genomic DNA as template were sequenced (page 10484, col. 2)(limitations of Claim 5). Drysdale teaches identifying 8 SNPs in the 5' UTR and 5 additional SNPs, three of which alter the encoded residues in the protein (Table 1, page 10484, col. 1)(limitations of Claim 16). The PCR products from the B2AR gene were placed in a vector and receptor expression was determined by radioligand binding, and mRNA levels were determine by using ribonuclease protection assays (page 1484, col. 2)(limitations of Claim 4, 8-9). Dresdale states that for both protein and mRNA expression, the results of the study are entirely consistent with the in vivo findings. Dresdale concludes that "the results indicate that the unique interactions of multiple SNPs within a haplotype ultimately affect biologic and therapeutic phenotype" (page 10488, col. 2).

Nandabalan et al. (herein referred to as Nandabalan) teaches a method of identifying functional SNPs in a gene. Nandabalan selects a candidate gene, namely tissue necrosis factor receptor (TNFR1). Nandabalan samples a "normal population" of individuals whose genomic DNA was isolated from an Index Repository containing 150 human individuals (page 5, lines 34-36). The human individuals comprise 112 unrelated individuals from African, Asian, Caucasian and Hispanic/Latino descent (Table 1, page 6)(limitations of Claim 2-3). Nandabalan teaches isolating nucleic acid from the individuals using PCR primers and identifying at least on SNP within the nucleic acid, namely 12 polymorphic sites (Table 5, page 38). Nandabalan also

identifies which of the mutations change the coding sequence, thereby which SNPs are functional. Nandabalan teaches that allele-specific oligonucleotide primes may be used to detect TNFR1 gene polymorphisms (page 19). Nandabalan teaches that the effects of the polymorphism identified on expression of TNFR1 may be investigated by preparing recombinant cells (page 15, lines 29-35). Nandabalan exemplifies amplifying various regions of the TNFR1 gene using primers (page 30). The PCR products were sequenced in both directions and analyzed for the presence of the polymorphisms (page 32-33)(limitations of Claims 4-5). Nandabalan also provides Table 4 indicating observed genotypes and haplotype pairs for TNFR1 (page 35). Figure 4 illustrates the SNPs within the coding sequence and Figure 5 illustrates the SNPs which alter the protein sequence (limitations of Claim 8, 16). The SNPs which alter the protein sequence are functional to the extent that the protein sequence is altered, i.e. modifies the functionality of the preselected candidate gene (as defined in the instant specification, paragraph 93).

Gu teaches a method of determining at least on functional SNP in a gene by selecting a candidate gene, namely P2X7 receptor, sampling a "normal population", isolating nucleic acid from the individuals, identifying at least on SNP and identifying functional SNPs. Gu teaches studying P2X7 by sequencing DNA coding for the carboxyl terminal tail of P2X7. Peripheral blood lymphocytes and monocytes were obtained from 45 normal subjects (page 6)(limitations of Claim 3). Genomic DNA was extracted using a primer pair and amplified (page 7). The amplified PCR products were sequenced using electrophoresis (page 7)(limitations of Claims 4-5). A nucleotide

substitution (A1513C) was found which cause a substitution for glutamic acid to alanine at amino acid position 496 (abstract, page 2). Gu teaches performing site directed mutagenesis to introduce a mutant (page 8). The functionality of the two sequences were analyzed (page 9). The function of the P2X7 receptors expressed on lymphocytes and monocytes was compared with the genotype at position 1513 of the P2X7 gene (page 10)(limitations of Claims 8-9). Cells transfected with germline and A1513C mutation were analyzed for surface expression by quantitating binding of FITC-conjugated mAb and the ATP-induced uptake of ethidium (page 11). Gu concludes that the "data in this study shows that the function of the human P2X7 receptor is affected by the single nucleotide mutation of adenine to cytosine at position 1513 of cDNA which changes glutamic acid to alanine at amino acid position 496" (page 13). The analysis demonstrated that homozygosity (C/C) for this polymorphic mutation let to almost complete loss of P2X7 function in leukocytes while herterozygosity (A/C) gave a function which was half that of cells with the germline P2X7 sequence (page 13).

Neither Dresdale, Nandabalan, nor Gu specifically teaches identifying a SNP using multiplexing method using denaturing high performance liquid chromatography (DHPLC).

However, Apffel et al. (herein referred to as Apffel) teaches a multiplexing method for identifying nucleic acids using denaturing liquid chromatography. Apffel teaches denaturing high performance liquid chromatography for separating heteroduplex and homoduplex nucleic acid sample in a mixture is described. The method of Apfell is directed to forming hybrid mixtures from more than one individual,

conducting DHPLC to compare the fragments by elution (forming one or more homogeneous groups comprising at least one mixture analyzed (col. 14-16)(limitations of Claims 6, 10). Apfell teaches that the multiplexed denaturing liquid chromatography method is a rapid method for identifying nucleic acids, specifically for distinguishing individual polymorphic nucleic acid molecules, involves relatively fewer steps and generates information relatively quickly (col. 3, lines 37-50). The ability to multiplex allows more samples to be analyzed in the same amount of time, increasing effective sample throughput and addresses the problem of the low throughput of liquid chromatography, particularly DHPLC (col. 7, lines 27-30; col. 7, lines 36-39). Apffel teaches the method involves spectral multiplexing. Apffel teaches that the method may be used in haplotying analysis (col. 14-15).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the SNP detection means taught in Dresdale, Nandabalan or Gu with the improved method of detecting multiple SNPs of Apffel. The ordinary artisan would have been motivated to have modified and improved the method of Dresdale, or Nandabalan or Gu by using the multiplexing method for identifying nucleic acids using denaturing liquid chromatography taught by Apffel. Apffel teaches the multiplexing method is a rapid method for identifying nucleic acids, specifically for distinguishing individual polymorphic nucleic acid molecules, involves relatively fewer steps and generates information relatively quickly (col. 3, lines 37-50). The ordinary artisan would have been motivated to be able to perform the analysis of the multiple individuals at multiple SNP sites quickly, to save time and reagents.

Therefore, using the multiplexing method of Apffel to identify a functional group of SNPs, as taught by Dresdale or Nandabalan or Gu, would have been obvious to the ordinary artisan at the time the invention was made.

10. Claims 7, 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dresdale et al (PNAS, Vol. 97, No. 19, pages 10483-10488, September 12, 2000) or Nandabalan et al. (WO 00/50436, August 31, 2000) or Gu et al. (JBC Papers in Press. Published on January 9, 2001 as Manuscript M010353200) in view of Apffel et al. (US Pat. 6,379,889, April 30, 2002) as applied to Claims 6, 10-11 above, and further in view of Oefner et al (US Pat. 5,795,976, August 18, 1998)

Neither Dresdale, Nandabalan, Gu nor Apffel specifically teach a method of identifying SNPs using DHPLC followed by sequencing or minisequencing.

However, Oefner et al. (herein referred to as Oefner) teaches a method of performing DHPLC to identify sequence variations followed by allele specific PCR (minisequencing) to confirm the sequence. Oefner teaches that polymorphic site identification was confirmed by subsequence conventional sequencing techniques (col. 34, lines 35-43).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have performed DHPLC to detect SNPs, as taught by Dresdal, Nadabalan, Gu and Apffel followed by sequencing as taught by Oefner. The ordinary artisan would have recognized that while the DHPLC method, which relies upon elution, is efficient and rapid, the elution mixture may contain additional sequences

in the specific elutes. Therefore, in order to confirm the results obtained by DHPLC, the ordinary artisan would have recognized that performing a sequencing reaction to confirm the results would have provided additional certainty for the identity of the sequence, as taught by Oefner. The ordinary artisan would have desired additional confidence and certainty to the results of the experiment and would have performed additional methods to confirm the identity of the sequence. Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to confirmed the polymorphic site identification using conventional sequencing techniques as specifically taught by Oefner.

Conclusion

11. No claims allowable over the art.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
Patent Examiner
August 7, 2003